(12) UK Patent Application (19) GB (11) 2 218 983 (13) A

(43) Date of A publication 29.11.1989

(21) Application No 8812596.8

(22) Date of filing 27.05.1988

(51) INT CL⁴
C07C 103/737, A61K 31/00, C07D 493/18 //
(C07D 493/18 307:00)

(52) UK CL (Edition J)
C2C CAA CKM C1175 C1200 C1204 C1210 C1480
C214 C22Y C225 C226 C227 C25Y C253 C280
C281 C30Y C34Y C342 C36Y C360 C361 C364
C366 C367 C368 C593 C603 C62X C628 C638
C65X C658 C668 C678 C80Y C802
U1S S2414

(56) Documents cited
None

(58) Field of search
UK CL (Edition J) C2C CKM
Chemical Abstracts (CAS On-line)

(71) Applicant
Pfizer Limited

(Incorporated in the United Kingdom)

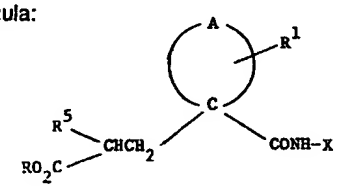
Ramsgate Road, Sandwich, Kent, CT13 9NJ,
United Kingdom

(72) Inventor
Dr John Christopher Danilewicz

(74) Agent and/or Address for Service
Dr J W Moore
Pfizer Limited, Ramsgate Road, Sandwich, Kent,
United Kingdom

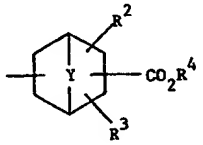
(54) Spiro-substituted glutaramides as diuretics

(57) Compounds of the formula:

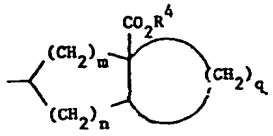


(I)

wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring ;
X is a bridged cyclic group of the formula:-



wherein Y is O, CH_2 or $(CH_2)_2$, or a bicyclic group of the formula:-



wherein each of n and m is independently 1 or 2 and q is an integer of from 3 to 5;
each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;
R^1 is H or C_1-C_4 alkyl;
R^2 and R^3 are each independently H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy;
and R^5 is a substituent;
and pharmaceutically acceptable salts thereof and bioprecursors thereof.
The compounds are diuretic agents having utility in the treatment of cardiovascular disorders such as hypertension and heart failure.

The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1982.

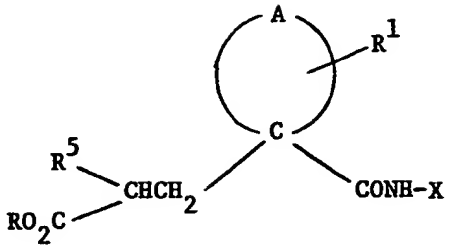
GB 2 218 983 A

2218983

This invention relates to a series of spiro-substituted glutaramide derivatives which are diuretic agents having utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as hypertension and heart failure.

The compounds are inhibitors of the zinc-dependent, neutral endopeptidase E.C.3.4.24.11. This enzyme is involved in the breakdown of several peptide hormones, including atrial natriuretic factor (ANF), which is secreted by the heart and which has potent vasodilatory, diuretic and natriuretic activity. Thus, the compounds of the invention, by inhibiting the neutral endopeptidase E.C.3.4.24.11, can potentiate the biological effects of ANF. Thus, in particular the compounds are diuretic agents having utility in the treatment of a number of disorders, including hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menières disease, hyperaldosteronism (primary and secondary), pulmonary oedema, ascites and hypercalciuria. In addition, because of their ability to potentiate the effects of ANF the compounds have utility in the treatment of glaucoma. As a further result of their ability to inhibit the neutral endopeptidase E.C.3.4.24.11 the compounds of the invention may have activity in other therapeutic areas including for example the treatment of asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), the modulation of gastric acid secretion and the treatment of hyperreninaemia.

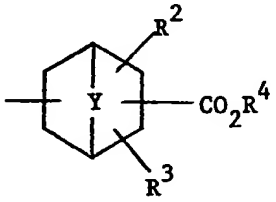
The compounds are of the formula:



(I)

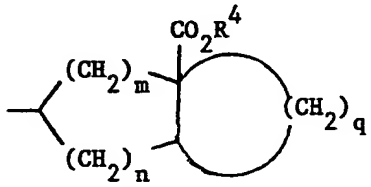
wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

X is a bridged cyclic group of the formula:-



wherein Y is O, CH_2 or $(CH_2)_2$,

or a bicyclic group of the formula:-



wherein each of n and m is independently 1 or 2 and q is an integer of from 3 to 5;

each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

R^2 and R^3 are each independently H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, C_1-C_6 alkoxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$ or a saturated heterocyclic group;

or C_1-C_6 alkyl substituted by one or more substituents chosen from halo, hydroxy, C_1-C_6 alkoxy, C_2-C_6 hydroxyalkoxy, C_1-C_6 alkoxy(C_1-C_6 alkoxy), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, aryloxy(C_1-C_4 alkoxy), heterocyclyl, heterocyclyloxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$, $-CONR^6R^7$, $-SH$, $-S(O)_pR^{10}$, $-COR^{11}$ or $-CO_2R^{12}$;

wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl (optionally substituted by hydroxy or C_1-C_4 alkoxy), aryl, aryl(C_1-C_4 alkyl), C_2-C_6 alkoxyalkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4 alkyl)-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4 alkyl), aryl(C_1-C_4 alkoxy), heterocycyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, aryl, heterocyclyl or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{11} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{12} is H or C_1-C_4 alkyl;

and p is 0, 1 or 2;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched-chain. The term aryl as used herein means an aromatic hydrocarbon group such as phenyl or naphthyl which may optionally be substituted with, for example, one or more OH, CN, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, carbamoyl, aminosulphonyl, amino, mono or di(C_1-C_4 alkyl) amino or (C_1-C_4 alkanoyl)amino groups. Halo means fluoro, chloro, bromo or iodo.

The term heterocyclyl means a 5 or 6 membered nitrogen, oxygen or sulphur containing heterocyclic group which, unless otherwise stated, may be saturated or unsaturated and which may optionally include a further oxygen or one to three nitrogen atoms in the ring and which may optionally be benzofused or substituted with for example, one or more halo, C_1-C_4 alkyl, hydroxy, carbamoyl, benzyl, oxo, amino or mono or di-(C_1-C_4 alkyl)amino or

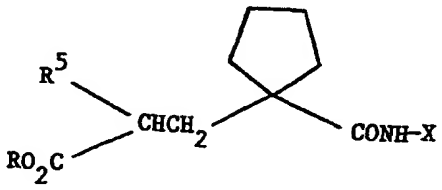
(C_1-C_4 alkanoyl)amino groups. Particular examples of heterocycles include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, isoindolinyl, quinolyl, quinoxalinyl, quinazolinyl and benzimidazolyl, each being optionally substituted as previously defined.

The compounds of formula (I) may contain several asymmetric centres and thus they can exist as enantiomers and diastereomers. The invention includes both the separated individual isomers as well as mixtures of isomers.

The pharmaceutically acceptable salts of the compounds of formula (I) containing an acidic centre are those formed with bases which form non-toxic salts. Examples include the alkali metal salts such as the sodium, potassium or calcium salts or salts with amines such as diethylamine. Compounds having a basic centre can also form acid addition salts with pharmaceutically acceptable acids. Examples include the hydrochloride hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate and tartrate salts.

The term bioprecursor in the above definition means a pharmaceutically acceptable biologically degradable derivative of the compound of formula (I) which, upon administration to an animal or human being, is converted in the body to produce a compound of the formula (I).

A preferred group of compounds of the f rmula (I) are those wherein A is $(CH_2)_4$ and R^1 is H, i.e. compounds of the formula (II) wherein R, R^5, and X are as previously defined for formula (I):



(II)

Also preferred are those compounds of formulae (I) and (II) wherein R and R^4 are both H (diacids) as well as biolabile mono and di-ester derivatives thereof wherein one or both of R and R^4 is a biolabile ester-forming group.

The term biolabile ester-forming group is well understood in the art as meaning a group which provides an ester which can be readily cleaved in the body to liberate the corresponding diacid of formula (I) wherein R and R^4 are both H. A number of such ester groups are well known, for example in the penicillin area or in the case of the ACE-inhibitor antihypertensive agents.

In the case of the compounds of formulae (I) and (II) such biolabile pro-drug esters are particularly advantageous in providing compounds of the formula (I) suitable for oral

administration. The suitability of any particular ester-forming group can be assessed by conventional animal or in vitro enzyme hydrolysis studies. Thus, desirably for optimum effect, the ester should only be hydrolysed after absorption, accordingly, the ester should be resistant to hydrolysis before absorption by digestive enzymes but should be readily hydrolyzed by for example, liver enzymes. In this way the active diacid is released into the bloodstream following oral absorption.

In addition to lower alkyl esters (particularly ethyl) and benzyl esters, suitable biolabile esters include alkanoyloxyalkyl esters, including alkyl, cycloalkyl and aryl substituted derivatives thereof, aryloxyalkyl esters, aroyloxyalkyl esters, aralkyloxyalkyl esters, arylesters, aralkylesters, and haloalkyl esters wherein said alkanoyl or alkyl groups have from 1 to 8 carbon atoms and are branched or straight chain and said aryl groups are phenyl, naphthyl or indanyl optionally substituted with one or more C_1-C_4 alkyl or C_1-C_4 alkoxy groups or halo atoms.

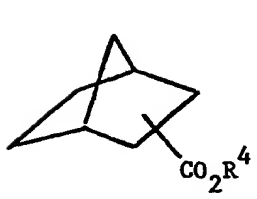
Thus examples of R and R^4 when they are biolabile ester-forming groups other than ethyl and benzyl include: 1-(2,2-diethylbutyryloxy)ethyl, 2-ethylpropionyloxymethyl 1-(2-ethylpropionyloxy)ethyl, 1-(2,4-dimethylbenzoyloxy)ethyl, α-benzoyloxybenzyl, 1-(benzoyloxy)ethyl, 2-methyl-1-propionyloxy-propyl, 2,4,6-trimethylbenzoyloxymethyl

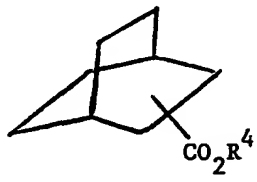
1-(2,4,6-trimethylbenzoyloxy)ethyl, pivaloyloxymethyl, phenethyl, phenpropyl, 2,2,2-trifluoroethyl, 1- or 2-naphthyl, 2,4-dimethylphenyl, 4-t-butylphenyl and 5-indanyl.

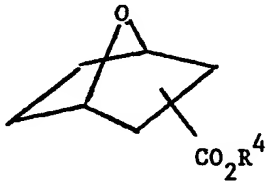
Of these a particularly preferred biolabile ester-forming group is 5-indanyl.

Compounds of the formulae (I) and (II) wherein one or both of R and R^4 are C_1-C_6 alkyl, particularly ethyl, or benzyl, are also active by virtue of their hydrolysis <u>in vivo</u>, and, in addition, are valuable intermediates for the preparation of the diacids wherein R and R^4 are both H.

Particular examples of compounds of the formula (I) wherein X is a bridged cyclic group include compounds wherein X is a group of the formula:-

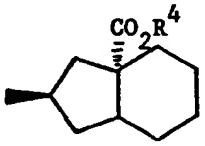






The above groups may be 2,5- or 2,6-linked, each attachment being of either endo or oxo stereochemistry.

Examples of compounds wherein X is a bicyclic group include in particular compounds wherein X is a group of the formula:



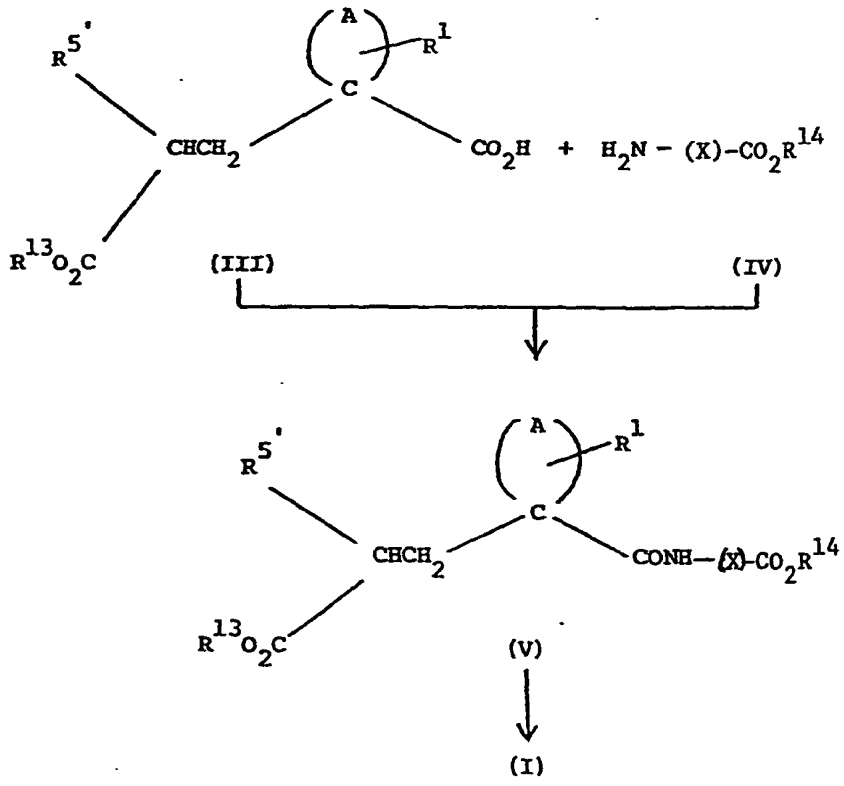
The group R^5 is preferably C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_5 alkynyl, C_5-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, C_1-C_4 alkylsulphonamido, or tetrahydrofuranyl or wherein R^5 is C_1-C_3 alkyl susbtituted by C_1-C_3 alkoxy, C_1-C_6 alkoxy(C_2-C_4 alkoxy), C_3-C_6 cycloalkyl, 4-pyridyl, 2-imidazolyl, C_2-C_4 alkanoyl, C_2-C_4 alkoxycarbonylamino, C_1-C_4 alkylsulphonyl, C_1-C_4 alkyl-sulphonamido, arylsulphonamido, heteroarylsulphonamido or benzoylamino. Thus particular and preferred examples of R^5 include methoxyethyl, 2-methoxyethoxymethyl, 4-aminobutyl and 2-methylsulphonylethyl.

Particularly preferred individual compounds of the invention include 3-{1-[6-endo-carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl} -2-(2-methoxyethyl)propanoic acid and 3-{1-[6-endo-carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl} -2-(2-methoxyethoxymethyl)propanoic acid, especially the dextrorotatory diastereoisomer of the latter compound wherein the bridged cyclic group X is resolved.

The comp unds of formula (I) are prepared by a number of different processes. The basic procedure involves coupling a partially protected spiro-substituted glutaric acid derivative to an amine to give the desired glutaramide. The carboxylic acid group in the amine, if free, or any reactive groups in R^5, may require protection during the coupling step and such protecting groups are removed in the final stage of the process.

The synthetic route is illustrated in scheme I wherein A, is as previously defined, $R^{5'}$ is as defined for R^5 with any reactive group therein protected if necessary, $(X)-CO_2R^{14}$ is as defined for X except that R^4 is R^{14}, and R^{13} and R^{14} are as defined for R and R^4 excluding H, or they are conventional carboxylic acid protecting groups:

Scheme 1



The reaction of the compounds of formula (III) and (IV) is achieved using conventional amide coupling techniques. Thus in one process the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a carbodiimide condensing agent, for example 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as N-methylmorpholine. The reaction is generally complete after a period of from 12 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water or filtration to remove the urea biproduct and evaporation of the solvent. The product may be further purified by crystallisation or chromatography, if necessary. The compounds of formula (V) include compounds of formula (I) wherein R and R^4 are C_1-C_6 alkyl or benzyl.

In some cases the coupled product, in protected form, may be subjected to conventional chemical transformation reactions to allow preparation of further compounds of formula (V). Thus for example compounds of formula (V) wherein $R^{5'}$ is a bromoalkyl group may be reacted with sodium azide and the product reduced by catalytic hydrogenation to yield the corresponding derivative wherein $R^{5'}$ is aminoalkyl. Similarly oxidation of compounds hwerein $R^{5'}$ contains a sulphide group yields the corresponding sulphoxide or sulphone derivative. Such transformations are entirely conventional and appropriate conditions and reagents for their performance will be well known t those skilled in the art as will other variations and possibilities.

The diesters of formula (V) may be further reacted to give the monoester or diacid derivatives of formula (I) wh rein one cr

both of R and R^4 are H. The conditions used will depend on the precise nature of the groups R^{13} and R^{14} present in the compound of formula (V) and a number of variations are possible. Thus for example when both of R^{13} and R^{14} are benzyl, hydrogenation of the product will yield the diacid of formula (I) wherein R and R^4 are both H. Alternatively if one of R^{13} and R^{14} is benzyl and the other is alkyl, hydrogenation will yield a monoester product. This can then be hydrolysed, if desired, to again yield the diacid product. When one of R^{13} and R^{14} is t-butyl, treatment of the compound of formula (V) with trifluoroacetic acid yields the corresponding acid. The diester product wherein R^{13} and R^{14} are benzyl or lower alkyl can also be treated with trimethylsilyl iodide to produce the dicarboxylic acid product. If some other carboxylic acid protecting group is used for R^{13} or R^{14} then clearly appropriate conditions for its removal must be employed in the final step to give the ester or diacid product of formula (I). In the case where the ring A or the substituent R^5 is unsaturated, the deprotection must be effected by non-reductive methods, thus for example if either of R and R^4 is benzyl, they may be removed by treatment with trimethylsilyl iodide.

As an alternative to the above procedure the coupling reaction is performed with an amine of the formula:-

$$H_2N\text{-}(X)\text{-}CH_2OH \qquad \text{--- (VI)}$$

The coupled product is deprotected as previously described and the product is then oxidised, for example by stirring with platinum in the presence of oxygen, to yield the corresponding acid of formula (I).

As well as removing any protecting group which may be present in $R^{5'}$, a number of chemical transformation reactions are possible on the final mono-ester or diacid products as previously described. In each case the product may be obtained as the free carboxylic acid or it may be neutralised with an appropriate base and isolated in salt form.

Compounds of the formula (I) wherein one or both R and R^4 is a biolabile ester forming group are prepared following similar procedures to those described above. Thus, in one variant of the process outlined in Scheme 1, a compound of formula (III) wherein R^{13} is a biolabile ester-forming group is coupled to the appropriate compound of formula (IV), wherein R^{14} is a benzyl group, and the product is hydrogenated to give the compound of formula (I) wherein R is a biolabile ester-forming group and R^4 is H.

The amines of formula (IV) and (VI) are in many cases novel compounds but they may be prepared from known starting materials by conventional synthetic procedures in accordance with literature precedents as illustrated in the Examples hereto. Thus for example the corresponding hydroxy-substituted bridged-cyclic carboxylate may be converted to the amine by sulphonylation followed by azide displacement and reduction, or a bicyclic lactone may be reduced by treatment with lithium aluminium hydride and the resulting diol converted to an aminoalcohol in a similar fashion.

The starting spiro-substituted glutaric acid mono esters of formula (III) may be prepared by a number of processes as described in European patent application 87310784.1.

As previously mentioned, the compounds of the invention are potent inhibitors of the neutral endopeptidase (E.C.3.4.24.11). This enzyme is involved in the breakdown of a number of peptide hormones and, in particular we have discovered that it is involved in the breakdown of atrial natriuretic factor (ANF). This hormone consists of a family of related natriuretic peptides, secreted by the heart, of which the major circulating form in humans is known to be the 28 amino-acid peptide referred to as α-hANP (see for example G. A. Sagnella and G. A. MacGreggor, Nature, 1984, 309, 666 and S. A. Atlas and others, Nature, 1984, 309, 717-725). Thus, the compounds of the invention, by preventing the degradation of ANF, by endopeptidase E.C.3.4.24.11 can potentiate its biological effects and the compounds are thus diuretic and natriuretic agents of utility in a number of disorders as previously described.

Activity against neutral endopeptidase E.C.3.4.24.11 is assessed using a procedure based on the assay described by J. T. Gafford, R. A. Skidgel, E. G. Erdos and L. B. Hersh, Biochemistry, 1983, 32, 3265-3271. The method involves determining the concentration of compound required to reduce by 50% the rate of release of radiolabelled hippuric acid from hippuryl-L-phenylalanyl-L-arginine by a neutral endopeptidase preparation from rat kidney.

The activity of the compounds as diuretic agents is determined by measuring their ability to increase urine output and sodium ion excretion in saline loaded conscious mice. In this test, male mice (Charles River CD1, 22-28 g) are acclimatised and starved overnight in metabowls. The mice are dosed intravenously via the tail vein, with the test compound dissolved in a volume of saline solution equivalent to 2.5% of body weight. Urine samples are collected each hour for two hours in pre-weighed tubes and analysed for electrolyte concentration. Urine volume and sodium ion concentration from the test animals are compared to a control group which received only saline.

For administration to man in the curative or prophylactic treatment of hypertension, congestive heart failure or renal insufficiency, oral dosages of the compounds will generally be in the range of from 10-1500 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2 to 300 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range 5 to 500 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above

dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

The compounds may be administered alone but may also be administered together with such other agents as the physician shall direct to optimise control of blood pressure or to treat congestive heart failure, renal insufficiency or other disorders in any particular patient in accordance with established medical practice. Thus the compounds can be co-administered with a variety of cardiovascular agents, for example with an ACE inhibitor such as captopril or enalapril to facilitate the control of blood pressure in treatment of hypertension; or with digitalis, or another cardiac stimulant or with an ACE inhibitor, for the treatment of congestive heart failure. Other possibilities

include co-administration with a calcium antagonist (e.g. nifedipine or diltiazem) a beta-blocker (e.g. atenolol) or an alpha-blocker (e.g. prazosin) as shall be determined by the physician as appropriate for the treatment of the particular patient or condition involved.

In addition to the above, the compounds may also be administered in conjunction with exogenous ANF, or a derivative thereof or related peptide or peptide fragment having diuretic/natriuretic activity or with other ANF-gene related peptides (e.g. as described by D. L. Vesely et al, Biochem. Biophys. Res. Comm., 1987, 143, 186).

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compounds of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, in particular in the treatment of hypertension, congestive heart failure or renal insufficiency in a human being.

The preparation of the compounds of the invention and of intermediates for use in their preparation is illustrated by the following Examples.

Purity of compounds was routinely monitored by thin layer chromatography. ^{1}H-N.M.R. spectra of all products were recorded using a Nicolet QE 300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

Methyl 6-exo-aminobicyclo[2,2,2]octane-2-endo-carboxylate hydrochloride

(a) A solution of 6-endo-hydroxybicyclo[2,2,2]octane-2-endo-carboxylic acid lactone (7.65 g; 50.3 mmole) in dioxan (100 ml) and 1N sodium hydroxide (200 ml) was allowed to stand at room temperature overnight. Most of the solvent was evaporated under reduced pressure at 40°C, and the residue was acidified to pH 5 with concentrated hydrochloric acid with ice cooling. The precipitate was collected by filtration and washed with water, to give 6-endo-hydroxybicyclo[2,2,2]octane-2-endo-carboxylic acid as a white solid (6.9 g, 80%), m.p. 125-125.5°C.

(b) Cesium carbonate (7.88 g; 24.2 mmole) in water (30 ml) was added to the above carboxylic acid (8.24 g; 48.4 mmole) in a 1:1 mixture of methanol and water (40 ml). The resulting clear solution was evaporated to dryness under vacuum, and the residue was dried azeotropically with toluene giving the cesium salt as a white solid. Methyl iodide (5 ml; 81 mmole) was added at room temperature to a stirred suspension of the cesium salt in dry dimethylformamide (40 ml). Water was added after 2.5 hours and the suspension was extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give an oil (8.8 g) which solidified on standing. Recrystallisation from hexane gave methyl 6-endo-hydroxybicyclo-[2,2,2]octane-2-endo-carboxylate as a white solid (7.52 g, 84%), m.p. 46-46.5°C. Found: C,65.09; H,8.83. $C_{10}H_{16}O_3$ requires C,65.19; H,8.75%.

(c) The above ester (7.11 g; 38.6 mmole) was added to an ice cold solution of 4-methylbenzenesulphonylchloride (11.04 g; 58 mmole) in dry pyridine (40 ml). After 0.5 hours the solution was allowed to warm to room temperature and, after standing overnight, the solvent was evaporated under vacuum. The residue was partitioned between ethyl acetate and water, and the organic phase was washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and water. Drying ($MgSO_4$), followed by evaporation of the solvent and recrystallisation from ethyl acetate-hexane gave methyl 6-endo-(4-methylbenzenesulphonyloxy)bicyclo[2,2,2]octane-2-endo-carboxylate as a white solid (11.65 g; 89%), m.p. 101-101.5°C. Found: C,60.29; H,6.57. $C_{17}H_{22}O_5S$ requires C,60.33; H,6.55%.

(d) The above 4-methylbenzenesulphonate (11.77 g, 34.8 mmole) was stirred under nitrogen with sodium azide (10 g; 150 mmole) in dry dimethylformamide (30 ml) for five days at 75°C. Most of the solvent was evaporated under vacuum keeping the temperature below 30°C. The residue was partitioned between ethyl acetate and water and the organic extract washed with water. Drying ($MgSO_4$) and evaporation of the solvent gave an oil which was chromatographed on silica. Elution with ethyl acetate, hexane (1:1) gave methyl-6-exo-azidobicyclo[2,2,2]octane-2-endo-carboxylate as an oil (4.28 g, 59%) contaminated with approximately 10% of methyl bicyclo[2,2,2]oct-5-ene-2-endo carboxylate.

(e) The azide of example 1(d) above (3.2 g) in methanol (30 ml) was hydrogenated over 10% palladium on charcoal catalyst (300 mg) at room temperature and 50 p.s.i. (3.45 bar). After five hours the mixture was filtered and evaporated to dryness. The residue was chromatographed on silica, eluting with a mixture of dichloromethane and methanol (98:2) followed by dichloromethane, methanol, 0.88 aqueous ammonia (94:5:1) to afford the required amine as an oil. An etherial solution of the product was treated with 4N HCl in dioxan to give the title hydrochloride which was isolated as a white solid (2.55 g) after recrystallisation from methanol-diethylether, m.p. 200-202°C. Found: C,54.13; H,8.47; N,6.17. $C_{10}H_{17}NO_2.HCl$, 0.1 H_2O requires C,54.21; H,8.28; N,6.32%.

EXAMPLE 2

Methyl-6-exo-aminobicyclo[2,2,2]octane-2-exo-carboxylate hydrochloride

(a) Diethyl diazocarboxylate (0.63 ml, 4 mmole) and diphenylphorylazide (0.86 ml; 4 mmole) were added simultaneously to an ice cold stirred solution of methyl 6-endo-hydroxybicyclo-[2,2,2]octane-2-exo-carboxylate (510 mg; 2.8 mmole) and triphenyl phosphine (1.05 g; 4 mmole) in dry tetrahydrofuran under nitrogen. After three hours the mixture was absorbed onto silica. Elution with a mixture of diethyl ether and hexane (2:8) gave crude product which was rechromatographed eluting with diethyl ether and hexane (1:9). The required methyl 6-exo-azidobicyclo[2,2,2]-octane- 2-exo-carboxylate was obtained as a clear liquid (400 mg, 69%). IR (film) 2100 cm^{-1}.

(b) The azide (390 mg, 1.87 mmole) from part (b) above was reduced following the procedure described in Example 1(e). The hydrochloride salt was recrystallised from a mixture of methylene chloride and diethyl ether to give methyl 6-exo-aminobicyclo-[2,2,2]octane-2-exo-carboxylate hydrochloride as a white solid (270 mg, 66%) m.p. 216-218°C. Found: C,54.44: H,8.63; N,6.32. $C_{10}H_{17}NO_2.HCl$ requires C,54.67; H,8.26; N,6.37%.

EXAMPLE 3

Methyl 5-endo-aminobicyclo[2,2,2]octane-2-endo-carboxylate hydrochloride

(a) Methyl 5-endo and 5-exo-hydroxybicyclo[2,2,2]octane-2-endo-carboxylate

Sodium borohydride (824 mg; 21.8 mmole) was added to an ice cold stirred solution of methyl 5-oxobicyclo[2,2,2]octane-2-endo-carboxylate (7.94 g; 43.6 mmole) in methanol (80 ml). After 2 hours the mixture was acidified to pH 4 with 2N hydrochloric acid and evaporated to a small volume under vacuum. The residue was partitioned between diethyl ether and water. The organic phase was washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation gave a crude mixture of isomers as a yellow oil (7.45 g). t.l.c. (silica; iso-propanol- methylene chloride (1:9)) Rf. 0.58 and 0.62. Chromatography on silica and eluting with diethyl ether and methylene chloride (1:9) gave an initial fraction (2.6 g), shown by g.l.c. to be 96% pure 5-endo isomer. ^{1}H-N.M.R. ($CDCl_3$) δ 3.80 (m H-C5), 3.72 (s CO_2CH_3). Following a

mixed fraction, a third fraction (1.64 g) was obtained which was shown by g.l.c. to be 94% pure 5-exo isomer. ^{1}H-N.M.R. ($CDCl_3$) δ 3.99 (m, H-C5) 3.68 (s, $-CO_2\underline{CH}_3$).

(b) The 5-exo-isomer from part (a) above (1.95 g; 10.58 mmole) was treated with 4-methylbenzenesulphonyl chloride in pyridine as described in Example 1(c). The crude product was chromatographed on silica, eluting with diethyl ether and hexane (4:6) to give methyl 5-exo-(4-methylbenzenesulphonyloxy)bicyclo-[2,2,2]octane-2-endo carboxylate as an oil (3.21 g, 90%). Found: C,60.29; H,6.53%. $C_{17}H_{22}O_5S$ requires C,60.33; H,6.55%.

(c) The above 5-exo-methylbenzenesulphonate (3.18 g, 9.4 mmole) was stirred under nitrogen with sodium azide (3.05 g; 47 mmole) in dry dimethylformamide (10 ml) at 55°C for eighteen hours and then at 75°C for forty-eight hours. Work up as described in Example 1(d) gave a pale yellow oil (1.95 g) which was chromatographed on silica. Elution with diethyl ether and hexane (5:95) gave methyl 5-endo-azidobicyclo[2,2,2]octane-2-endo carboxylate as a clear liquid (950 mg; 48%). Found: C,57.15; H,7.40; N,20.22. $C_{10}H_{15}N_3O_2$ requires C,57.40; H,7.23; N,20.08%.

(d) The above azide (940 mg; 4.49 mmole) was reduced as described in Example 1(e). The crude hydrochloride was recrystallised from methanol/diethyl ether to give the title amine as a white solid (430 mg, 44%), m.p. 156-7°C. Found: C,54.79; H,8.36; N,6.37. $C_{10}H_{17}NO_2$.HCl requires C,54.67; H,8.26; N,6.37%.

EXAMPLE 4

Methyl-5-exo-aminobicyclo[2,2,2]octane-2-endo-carboxylate hydrochloride

(a) The 5-endo-hydroxy compound from Example 3(a) (3.1 g; 16.82 mmole) was treated with 4-methylbenzenesulphonyl chloride (4.81 g; 25.2 mmole) in dry pyridine as described in Example 1(c). The crude product was chromatographed on silica, eluting with diethyl ether and hexane (4:6) to give methyl-5-endo-(4-methylbenzenesulphonyloxy)bicyclo[2,2,2]octane-2-endo-carboxylate as an oil (5.20 g, 91%). Found: C,60.29; H,6.54. $C_{17}H_{22}O_5S$ requires C,60.33; H,6.55%.

(b) The above 5-endo-methylbenzenesulphonate (5.15 g; 15.2 mmole) was stirred under nitrogen with sodium azide (4.94 g; 76 mmole) in dry dimethylformamide (15 ml) at 55°C for eighteen hours and then at 75°C for thirty hours. Work up as described in Example 1(d) gave a pale yellow liquid which was chromatographed on silica. Elution with diethyl ether and hexane (5:95) gave methyl-5-exo-azidobicyclo[2,2,2]octane-2-endo-carboxylate, as a clear liquid (1.9 g, 61%). Found: C,57.17; H,7.26; N,20.02. $C_{10}H_{15}N_3O_2$ requires C,57.40; H,7.23; N,20.08%.

(c) The above azide (1.9 g; 9.1 mmole) was reduced as described in Example 1(e). The crude hydrochloride was recrystallised from methanol/diethyl ether to give the title amine as a white solid (840 mg, 42%), m.p. 228-229°C. Found: C,54.64; H,8.45; N,6.31. $C_{10}H_{17}NO_2.HCl$ requires C,54.67; H,8.26; N,6.37%.

EXAMPLE 5

1H-2β-Amino-2,3,3aα,4,5,6,7,7aα-octahydroindene-3aα-carboxylic acid ethyl ester

(a) 2H-2-Oxo-1,3,3aα,4,5,6,7,7aα-octahydroindene-3aα-carboxylic acid ethyl ester (2.9 g; 13.8 mmole) [W. Dauben et al., J. Org. Chem., 1961, 26, 297] in tetrahydrofuran (30 ml) was added dropwise under nitrogen to a stirred 1M solution of lithium trisiamylborohydride in tetrahydrofuran (15.2 ml; 15.2 mmole) at -70 to -60°C. After two hours the mixture was allowed to warm to ambient temperature and left to stand for eighteen hours. The mixture was then cooled to 10°C. Water (1 ml), ethanol (3.4 ml), 6N aqueous sodium hydroxide (2.3 ml) and 30% aqueous hydrogen peroxide (3.4 ml) were added in succession. After five minutes the aqueous phase was saturated with potassium carbonate, diethyl ether and saturated sodium chloride solution were added and the organic layer was separated off. The aqueous phase was re-extracted with diethyl ether and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give an oil which was chromatographed on silica. Gradient elution using hexane and ethyl acetate (3:7 to 1:1) gave 1H-2β-hydroxy-2,3,3aα-4,5,6,7,7aα-octahydro-indene-3aα-carbonyl acid ethyl ester as an oil (2.52 g; 86%). Found: C,67.70; H,9.67. $C_{12}H_{20}O_3$ requires C,67.89; H,9.50%.

(b) Diethyl azodicarboxylate (2.47 ml; 15.7 mmole) in tetrahydrofuran (15 ml) was added dropwise at 10°C to a stirred solution of the hydroxy acid from part (a) (2.22 g; 10.5 mmole), methyl 4-methylbenzenesulphonate (2.43; 13.1 mmole) and triphenyl

phosphine (3.43 g; 13.1 mmole) in tetrahydrofuran (25 ml). After stirring for 20 hours at ambient temperature, the mixture was evaporated to dryness, absorbed onto silica and chromatographed on silica. Gradient elution starting from hexane and methylene chloride (3:7) to neat methylene chloride gave 1H-2∝-(4-methylbenzensulphonyloxy)-2,3,3a∝,4,5,6,7,7a∝-octahydroindene-3a∝-carboxylic acid ethyl ester as a clear oil (2.01 g; 58%). Found: C,62.27; H,7.27. $C_{19}H_{26}O_5S$ requires C,62.27; H,7.15%.

(c) The product from part (b) above (1.99 g) was treated with sodium azide and reduced as described in Example 4 to give the crude amine which was chromatographed on silica. Gradient elution with increasing proportions of ethanol in methylene chloride (0 to 20%) gave pure title product as an oil (770 mg; 62% overall). Found: C,65.85; H,9.74; N,6.32. $C_{12}H_{21}NO_2$,0.5 H_2O requires C,65.42; H,10.07; N,6.36%.

EXAMPLE 6

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid benzyl ester

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (958 mg; 5 mmole) was added to an ice cold stirred mixture of 3-(1-carboxycyclopentyl)-2-(2-methoxyethyl)propanoic acid benzyl ester (836 mg; 2.5 mmole), methyl 6-exo-aminobicyclo[2,2,2]-octane-2-endo carboxylate hydrochloride (550 mg; 2.5 mmole), 1-hydroxybenzotriazole (337 mg; 2.5 mmole) and N-methylmorpholine (834 mg; 8.25 mmole) in dry methyl ne chloride (10 ml). After 0.5

hours the mixture was allowed to attain room temperature and stirred for a further eighteen hours. The mixture was diluted with methylene chloride, washed in succession with water, 1N hydrochloric acid, saturated aqueous sodium bicarbonate and water, and dried ($MgSO_4$). Evaporation gave an oil which was chromatographed on silica. Elution with ethyl acetate and hexane (3:7) gave the title diester as a gum (1.08 g; 85%). Found: C,69.42; H,8.29; N,2.75. $C_{29}H_{41}NO_6$, 0.11 $CH_3CO_2C_2H_5$ requires C,69.71; H,8.27; N,2.80%.

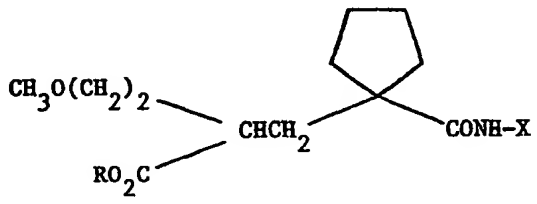
EXAMPLE 7

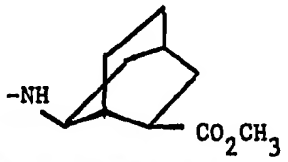
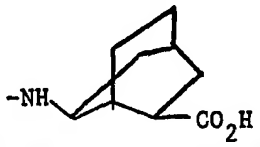
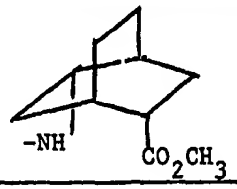
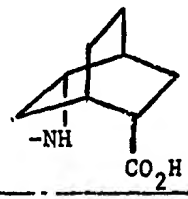
3-{1-[6-endo-carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl}-2-(2-methoxyethyl)propanoic acid

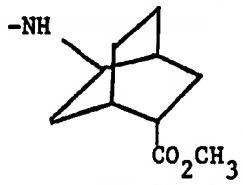
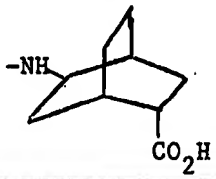
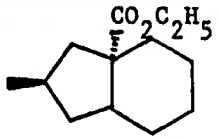
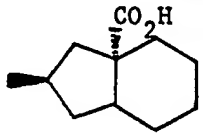
The diester from Example 6 (980 mg; 1.96 mmole) in methanol (18 ml) and water (12 ml) was hydrogenated over 5% palladium on charcoal catalyst (100 mg) at 50 p.s.i. (3.45 bar). After four hours the mixture was filtered through avicel, washing with methanol, and evaporated to dryness. The residue was partitioned between diethyl ether and 1N sodium hydroxide (4 ml). The aqueous phase was separated and the ether phase was again extracted with 1N sodium hydroxide (4 ml). The combined aqueous extracts were allowed to stand at room temperature for eighteen hours and then acidified with 2N hydrochloric acid. The suspension was extracted with methylene chloride, the extract washed with saturated aqueous sodium chloride solution and dried ($MgSO_4$). Evaporation of the solvent gave the required diacid as a white foam (705 mg, 91%). Found: C,63.50; H,8.61; N,3.31. $C_{21}H_{33}NO_6$ requires C,63.77; H,8.41; N,3.54%.

EXAMPLES 8 - 15

The following compounds were prepared from the appropriate amine of Examples 2 to 5 following the coupling and deprotection procedures of Examples 6 and 7.



Example	R	-NH-X	Form Isolated	Analysis % (Theoretical in brackets) C	H	N
8	$CH_2C_6H_5$		gum	69.42 (69.71	8.40 8.27	2.57 2.80)
9	H		foam (0.5 H_2O)	62.51 (62.36	8.36 8.47	3.41 3.46)
10	$CH_2C_6H_5$		oil	69.36 (69.71	8.34 8.27	3.15 2.80)
11	H		foam (0.4 H_2O)	62.58 (62.63	8.33 8.46	3.48 3.48)

Example	R	-NH-X	Form Isolated	Analysis % (Theoretical in brackets) C	H	N
12	$CH_2C_6H_5$		oil	69.70 (69.71	8.42 8.27	2.73 2.80)
13	H		foam (0.4 H_2O)	62.71 (62.63	8.49 8.46	3.47 3.48)
14	$CH_2C_6H_5$		oil	70.79 (70.56	8.79 8.60	2.66 2.66)
15	H		foam (0.33 H_2O)	63.48 (63.59	8.53 8.65	3.30 3.37)

EXAMPLE 16

6-endo-Hydroxymethylbicyclo[2,2,1]heptan-2-exo-amine hydrochloride

(a) A solution of 6-endo-hydroxybicyclo[2,2,1]heptane-2-endo-carboxylic acid lactone (11.0 g; 79.7 mmole) in diethyl ether (150 ml) was added dropwise over 0.5 hours under nitrogen to a stirred ice cooled suspension of lithium aluminium hydride (3.02 g; 79.7 mmole) in dry diethyl ether (50 ml), keeping the temperature between 10 and 20°C. The mixture was then stirred at room temperature for 2 hours, saturated aqueous ammonium chloride (20 ml) was carefully added followed by solid ammonium chloride (15 g) and magnesium sulphate to produce a granular suspension. The mixture was filtered, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a white solid (11.15 g). Chromatography on silica, eluting with diethyl ether and recrystallisation from ether and hexane gave 6-endo-hydroxy-methylbicyclo[2,2,1]heptan-2-endo-ol as a white solid (9.49; 84%). An analytical sample had m.p. 118-120°C. Found: C,67.87; H,10.24. $C_8H_{14}O_2$ requires C,67.57; H,9.93%.

(b) (1,1-Dimethylethyl)dimethylsilylchloride (10.98 g; 72.8 mmole) in dry methylene chloride (45 ml) was added with ice cooling to a stirred solution of the above diol (9.42 g; 66.2 mmole), triethylamine (7.37 g; 72.82 mmole) and 4-dimethylaminopyridine (325 mg, 2.65 mmole) in methylene chloride (55 ml). After stirring at room temperature for one and a half hours the solution was washed in succession with water, saturated aqueous ammonium chloride and water. Drying ($MgSO_4$) and evaporation under reduced pressure gave a pale yellow liquid.

Chromatography on silica eluting with diethyl ether and hexane (1:9 - 1:1) gave 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl]bicyclo[2,2,1]heptan-2-endo-ol as a clear liquid (16.2 g; 95%). Found C,65.05; H,10.98; $C_{14}H_{28}O_2Si$ requires C,65.57; H,11.00%.

(c) The carbinol from part (b) above (13.12 g; 51.6 mmole) was treated with sodium azide as described in Example 2(a) to give 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl]bicyclo[2,2,1]-heptane-2-exo-azide (5.83 g, 40%) as an oil. I.R. (film) ν max 2100 cm^{-1}. Found: C,60.25; H,9.83; N,14.11. $C_{14}H_{27}N_3OSi$ requires C,59.74; H,9.67; N,14.93%.

(d) A 1N solution of tetrabutylammonium fluoride in tetrahydrofuran (30 ml) was added to an ice cooled solution of the azide from part (c) above (5.8 g; 20.6 mmole) in dry tetrahydrofuran (30 ml). After two hours at 5°C the solution was diluted with diethyl ether and washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation gave a clear volatile liquid which was chromatographed on silica. Elution with diethyl ether and hexane (1:1) gave 6-endo-hydroxymethylbicyclo[2,2,1]-heptane-2-exo-azide as a liquid (2.95 g; 86%). I.R. (film) ν max 2100 cm^{-1}. Found: C,57.44; H,7.91; N,24.81. $C_8H_{13}N_3O$ requires C,57.46; H,7.84; N,25.13%.

(e) The azide from part (d) above was reduced as described in Example 1(e) but using ethanol as solvent. The crude hydrochloride was recrystallised from a mixture of methanol and diethyl ether to give the title amine as a white solid (3.24 g; 85%) m.p. 158-9°C. Found: C,53.91; H,9.23; N,7.70. $C_8H_{15}NO.HCl$ requires C,54.08; H,9.08; N,7.88%.

EXAMPLE 17

6-endo-Hydroxymethyl-7-oxabicyclo[2,2,1]heptan-2-exo-amine

(a) 6-endo-Hydroxy-5-exo-iodo-7-oxabicyclo[2,2,1]heptane-2-endo-carboxylic acid lactone (83.43 g; 0.316 mole) dissolved in tetrahydrofuran (250 ml) and ethyl acetate (500 ml) containing triethylamine (35.2 g; 0.35 mole) was hydrogenated over platinum (from platinum oxide, 4 g) at room temperature and 50 p.s.i. (3.45 bar). After six hours water was added and the mixture was filtered through avicel. The aqueous phase was extracted (x 2) with ethyl acetate, and the combined organic solutions were washed in succession with, 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate, sodium metabisulphite solution and water. Drying ($MgSO_4$) and evaporation gave a white solid (35.2 g). Recrystallisation from ethyl acetate and hexane gave 6-endo-hydroxy-7-oxabicyclo[2,2,1]heptane-2-endo-carboxylic acid lactone (28.18 g; 63%), m.p. 89.5-90°C. Found: C,60.11; H,5.83. $C_7H_8O_3$ requires C,59.99; H,5.75%.

(b) The lact ne from part (a) above (14.1 g; 0.1 mole) was reduced with lithium aluminium hydride following the procedure in Example 16(a). The crude product was chromatographed on silica, eluting with ethyl acetate, to give 6-endo-hydroxymethyl-7-oxabicyclo[2,2,1]heptan-2-endo-ol as a hygroscopic waxy solid (11.7 g; 81%). Found: C,58.31; H,8.59. $C_7H_{12}O_3$ requires C,58.31; H,8.39%.

(c) The diol from part (b) above (11.63 g; 80.7 mmole) was treated with (1,1-dimethylethyl)dimethylsilylchloride as described in Example 16(b). Chromatography of the product on silica, eluting with diethyl ether and hexane (1:1 - 2:1), gave 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl]-7-oxabicyclo[2,2,1]-heptan-2-endo-ol as a clear liquid (18.58 g; 89%). Found: C,60.78; H,10.09. $C_{13}H_{26}O_3Si$ requires C; 60.42; H,10.14%.

(d) The carbinol from part (c) above (13.1 g; 50.69 mole) was treated with 4-methylbenzensulphonyl chloride as described in Example 1(c) except that the reaction mixture was allowed to stand at room temperature for five days. The crude product was chromatographed on silica, eluting with a gradient of diethyl ether and hexane (2:8 - 4:6), to give 6-endo-[(1,1-dimethyl-ethyl)dimethylsilyloxymethyl)]-7-oxabicyclo[2,2,1]heptan-2-endo-ol 4-methylbenzenesulphonate as a clear oil (15.84 g; 76%). Found: C,58.20; H,7.90. $C_{20}H_{32}O_5SiS$ requires C,58.22; H,7.82%.

(e) The 4-methylbenzenesulphonate from part (d) above (16.79 g; 40.67 mmole) and sodium azide (5.3; 81.3 mmole) in dry dimethylformamide (40 ml) were stirred under nitrogen for two days at 105°C.

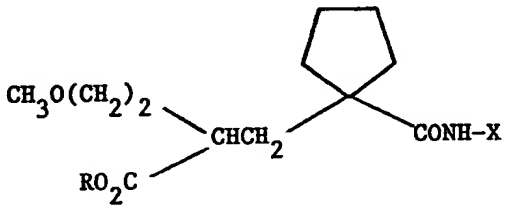
A further amount of sodium azide (2.65 g) was added, and stirring continued for six days at 105-110°C. The mixture was cooled, diluted with water and extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was chromatographed on silica. Gradient elution with diethyl ether and hexane (15:85 - 1:1) gave an initial fraction containing the required 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl)]-7-oxabicyclo-[2,2,1]heptan-2-exo-azide (2.54 g; 22%) as a clear liquid. Continued elution gave recovered starting material (10.7 g; 63%).

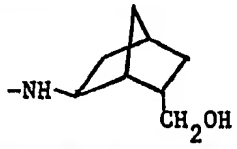
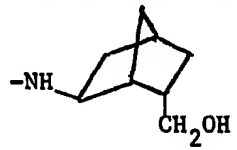
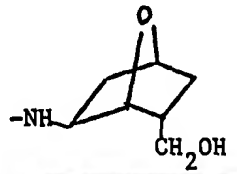
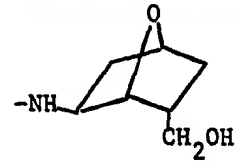
(f) The above azide (2.54 g; 8.96 mmole) was treated with tetrabutylammonium fluoride as described in Example 16(d) to yield 6-endo-hydroxymethyl-7-oxabicyclo[2,2,1]heptan-2-exo-azide as an oil (1.33 g; 88%). I.R. (film) ν max. 3400 and 2100 cm^{-1}. Found: C,49.53; H,6.63; N,24.60. $C_7H_{11}O_2N_3$ requires C,49.69; H,6.55; N,24.84%.

(g) The azide from part (f) above (1.3 g; 7.7 mmole) was hydrogenated in ethanol (25 ml) over 10% palladium on charcoal (100 mg) at 50 p.s.i. (3.46 bar). After three hours the suspension was filtered through avicel and the solvent evaporated to give a white solid which was recrystallised from a mixture of methylene chloride and diethyl ether to give the title amine (930 mg; 84%), m.p. 102-103.5°C. Found: C,58.43; H,9.53; N,9.72. $C_7H_{13}NO_2$ requires C,58.72; H,9.15; N,9.78%.

EXAMPLES 18 - 21

The amines of formula (VI) from Examples 16 and 17 were coupled to 3-(1-carboxycyclopentyl)-2-(2-methoxyethyl)propanoic acid benzyl ester and the products hydrogenated to remove the benzyl group following the procedures of Examples 6 and 7 to yield the following compounds:



Example	R	-NH-X	Form Isolated	Analysis % (Theoretical in brackets) C	H	N
18	$CH_2C_6H_5$		gum	70.64 (70.86	8.75 8.59	3.39 3.06)
19	H		foam (0.3 H_2O)	64.34 (64.42	9.00 9.08	3.79 3.76)
20	$CH_2C_6H_5$		oil	65.90 (66.03	7.93 7.91	2.92 2.94)
21	H		gum (0.6 H_2O)	59.98 (60.01	8.63 8.53	3.79 3.68)

EXAMPLE 22

3-{1-[6-endo-Carboxybicyclo[2,2,1]heptane-2-exo-carbamoyl]-cyclopentyl}-2-(2-methoxyethyl)propanoic acid

3-{1-[6-endo-Hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid from Example 19 (350 mg; 0.95 mmole) dissolved in water (30 ml) containing sodium bicarbonate (240 mg; 2.8 mmole) was vigorously stirred over platinum (from platinum oxide 350 mg; 1.5 mmole) under oxygen at 40°C. After two hours the suspension was filtered through avicel. The filtrate was evaporated to a small volume under reduced pressure, saturated with salt and acidified with 2N hydrochloric acid. The suspension was extracted with ethyl acetate and the extract washed with saturated salt solution, dried ($MgSO_4$) and evaporated to give the title diacid as a white foam. (365 mg; 97%). Found: C,61.78; H,8.16; N,3.77. $C_{20}H_{31}NO_6$, 0.1 CH_2Cl_2, 0.1 $CH_3CO_2C_2H_5$ requires C,61.74; H,8.09; N,3.51%.

EXAMPLE 23

3-{1-[6-endo-Carboxy-7-oxabicyclo[2,2,1heptane-2-exo-carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid

The carbinol from Example 21 was oxidised following the procedure of Example 22 above to yield the title compound as a white foam. Found: C,58.32; H,7.82; N,3.39. $C_{19}H_{29}NO_7$, 0.1 CH_2CH_2 requires C,58.53; H,7.51; N,3.57%.

EXAMPLE 24

3-{1-[6-endo-Methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(2-methylthioethyl)propanoic acid benzyl ester

3-(1-Carboxycyclopentyl)-2-(2-methylthioethyl)propanoic acid benzyl ester was coupled to methyl 6-exo-aminobicyclo[2,2,2]-octane-2-endo-carboxylate (from Example 1) following the procedure of Example 6 to yield the title diester as an oil. Found: C,65.21; H,7.68; N,2.28. $C_{29}H_{41}NO_5S.H_2O$ requires C,65.27; H,8.12; N,2.62%.

EXAMPLE 25

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(2-methylsulphonylethyl)propanoic acid benzyl ester

The methylthio compound of Example 24 (220 mg; 0.43 mmole) was stirred with 3-chloroperbenzoic acid (184 mg) in methylene chloride for three hours at room temperature. The solvent was evaporated and the residue was partitioned between 5% aqueous sodium bicarbonate and diethyl ether. The ether extract was dried ($MgSO_4$) and the solvent evaporated. The crude product (220 mg) was chromatographed on silica, eluting with a gradient of ethyl acetate and hexane (1:4 — 1:2) to give the pure title product as a gum (75 mg; 33%). Found: C,63.89; H,7.96; N,2.48. $C_{29}H_{41}NO_7S$ requires C,63.60; H,7.55; N,2.56%.

EXAMPLE 26

3-{1-[6-endo-Carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl} -2-(2-methylsulphonylethyl)propanoic acid

Hydrogenation and hydrolysis of the product of Example 25 above following the procedure of Example 7 gave the title bis-acid as a white foam. Found: C,56.31; H,8.61; N,3.11. $C_{21}H_{33}NO_7S$ requires C,56.87; H,7.50; N,3.16%.

EXAMPLE 27

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl} -2-(4-bromobutyl)propanoic acid 1,1-dimethylethyl ester

3-(1-Carboxycyclopentyl)-2-(4-bromobutyl)propanoic acid 1,1-dimethylethyl ester was coupled to methyl 6-exo-amino-bicyclo[2,2,2]octane-2-endo-carboxylate (from Example 1) following the procedure of Example 6 to yield the title diester as an oil.

EXAMPLE 28

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl} -2-(4-azidobutyl)propanoic acid 1,1-dimethylethyl ester

The bromo compound from Example 27 above (780 mg, 1.44 mmole) and sodium azide (195 mg, 3 mmole) were stirred in dry dimethylformamilde (3 ml) at 50°C under nitrogen for two days. The mixture was diluted with water and extracted with diethyl

ether. The extract was washed with water, dried ($MgSO_4$) and evaporated to give a gum which was chromatographed on silica. Elution with diethyl ether and hexane gave the title azide as an oil (350 mg; 48%). Found: C,64.44; H,8.84; N,10.85. $C_{27}H_{44}N_4O_5$ requires C,64.24; H,8.79; N,11.10%.

EXAMPLE 29

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(4-aminobutyl)propanoic acid 1,1-dimethylethyl ester

The azide product from Example 28 above was reduced as described in Example 1(e). The crude product was chromatographed on silica by gradient elution using methanol and methylene chloride (1:99 - 7:93). The pure title product was obtained as a gum (208 mg; 64%).

EXAMPLE 30

3-{1-[6-endo-Carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl}-2-(4-aminobutyl)propanoic acid

The diester product of Example 29 above (208 mg; 0.43 mmole) was allowed to stand at room temperature with trifluoroacetic acid (1 ml) in methylene chloride (1 ml) for four hours. The solvent was evaporated under vacuum, and the residue was triturated with warm diethyl ether. The insoluble salt was dissolved in 1N sodium hydroxide (3 ml), and allowed to stand at room temperature for four hours and at 0°C for eighteen hours. The solution was passed

through ion exchange resin (Bio-Rad AG 50W-X8, 4.0 g) and the column eluted with 2% aqueous pyridine to give the title diacid as a white foam (146 mg, 79%). Found: C,61.93; H,8.58; N,6.42. $C_{22}H_{36}N_2O_5$, 0.5 H_2O, 0.15 CH_2Cl_2 requires C,61.83; H,8.73; N,6.51%.

EXAMPLE 31

N-(1-Naphthoyl)-(S)-prolinol

1-Naphthoyl chloride (19.0 g; 0.1 mmole) was added dropwise over five minutes to a stirred ice cooled solution of (S)-prolinol (10.1 g; 0.1 mmole) and N-methylmorpholine (11.0 g; 0.1 mmole) in dry methelene chloride (100 ml). After stirring at room temperature for three hours, ice was added and the solvent was evaporated under reduced pressure. The residue was partitioned between diethyl ether and water and the organic phase was washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying over $MgSO_4$ and evaporation gave a gum which was chromatographed on silica. Elution with ethyl acetate gave the title product (21.33 g; 84%). $[\alpha]_D^{25}$ -111.3°, $[\alpha]_{365}^{25}$ -405.0° (c. 1.15, CH_2Cl_2). Found: C,73.60; H,6.76; N,5.27. $C_{16}H_{17}NO_2.0.25\ H_2O$ requires C,73.96; H,6.79; N,5.39%.

EXAMPLE 32

1-(1-Naphthoyl)-2(S)-bromomethylpyrrolidine

Triphenylphosphine (26.3 g; 0.1 mole) was added to an ice cold stirred solution of N-(1-naphthoyl)-(S)-prolinol (21.33 g, 83.5 mmole) and carbon tetrabromide (33.1 g; 0.1 mole) in dry methelene chloride (220 ml). The mixture was allowed to warm to

room temperature over half an hour, stirred for a further hour, and the solvent was evaporated under reduced pressure. The residue was extracted (x 8) with diethyl ether. Direct application of the solutions to a silica column followed by elution with diethyl ether gave the title bromo derivative as gum (20.2 g; 72%). $[\alpha]_D^{25}$ - 126.6°, $[\alpha]_{365}^{25}$ -496.5° (c = 1.21; CH_2Cl_2). Found: C,57.11; H,4.76; N,4.15. $C_{16}H_{16}BrNO$ requires C,57.50; H,4.82; N,4.19%.

EXAMPLE 33

6(R and S)-endo-Hydroxybicyclo[2,2,2]octane-2(S and R)-endo-carboxylic acid. N-(1-naphthoyl)-2(S)-prolinol ester

6-endo-Hydroxybicyclo[2,2,2]octane-2-endo-carboxylic acid lactone (5.02 g; 33 mmole) was heated at 100°C with 1.02 N cesium hydroxide (32.3 ml; 33 mmole) and dioxan (15 ml). After three hours the solution was allowed to cool to room temperature and, after standing overnight, the solvent was evaporated under reduced pressure. The residue was dried azeotropically with toluene (x 2) and triturated with hot diethyl ether. The resulting cesium salt (3.93 g; 13 mmole) and 1-(1-naphthoyl)-2(S)-bromomethylpyrrolidine (4.34 g; 13 mmole) were stirred for two days at room temperature in dry dimethylformamide (10 ml). The mixture was diluted with water, extracted with ethyl acetate, and the organic extract was washed in succession with saturated aqueous sodium bicarbonate, and water. Drying ($MgSO_4$) and evaporation under reduced pressure gave a yellow gum which was chromatographed on silica. Elution with acetone and toluene (3:7) allowed the diastereoisomers to be separated as gums.

Isomer I t.l.c. (acetone, toluene, 3:7) Rf. 0.32. $[\alpha]_D^{25}$ - 78.6°, $[\alpha]_{365}^{25}$ -336.0° (c = 1.06, CH_2Cl_2). Found: C,73.98; H,7.31; N,3.39. $C_{25}H_{29}NO_4.0.1\ CH_3C_6H_5$ requires C,74.08; H,7.21; N,3.36%.

Isomer II t.l.c. Rf. 0.29 $[\alpha]_D^{25}$ - 58.8°, $[\alpha]_{365}^{25}$ -258.7° (c = 1.03, CH_2Cl_2). Found: C,73.75; H,7.31; N,3.35. $C_{25}H_{29}NO_4$. 0.1 $CH_3C_6H_5$ requires C,74.08; H,7.21; N,3.36%.

EXAMPLE 34

6-(S or R)-exo-Aminobicyclo[2,2,2]octane-2(R or S)-endo-carboxylic acid N-(1-naphthoyl)-2(S)-prolinol ester hydrochloride

Isomer II from Example 33 above (1.16 g; 2.85 mmole) was treated with 4-methylbenzenesulphonyl chloride followed by reaction of the product with sodium azide and reduction of the azide product following the procedures of Example 1(c) to (e), to yield the title amine as an amorphous solid which failed to crystallise. T.l.c. (dichloromethane, methanol, acetic acid, 90:10:1) Rf 0.3. $[\alpha]_D^{25}$ -12.9°, $[\alpha]_{365}^{25}$ -93.9° (c = 0.026, methanol).

EXAMPLE 35

(+)-3-{1-[6(S or R)-endo-Carboxybicyclo[2,2,2]octane-2(R or S)-exo-carbamoyl]cyclopentyl}-2(R,S)-(methoxyethoxymethyl)propanoic acid

The product from Example 34 above was coupled to 3-(1-carboxycyclopentyl)-2-(2-methoxyethoxymethyl)propanoic acid 1,1-dimethylethyl ester following the procedure of Example 6. The coupled diester was obtained as a foam. Found: C,69.91; H,8.11; N,3.92. $C_{42}H_{58}N_2O_8$ requires C,70.17; H,8.13; N,3.90%.

Treatment of the product with trifluor acetic acid followed by sodium hydroxide according to the procedure of Example 30 to remove the 1,1-dimethylethyl and N-(1-naphthoyl)-2(S) prolinol ester groups gave the title dicarboxylic acid as its dextrorotatory diastereoisomer. $[\alpha]_D^{25}$ +53.9°, $[\alpha]_{365}^{25}$ + 180.60° (c = 1.2, CH_2Cl_2). Found: C,61.59; H,8.58; N,3.16. $C_{22}H_{35}NO_7$, 0.2 H_2O requires C,61.58; H,8.31; N,3.26%.

It will be appreciated from the foregoing that what we will claim may include the following:-

(1) The compounds of the formula (I) and pharmaceutically acceptable salts thereof and bioprecursors therefor.

(2) Processes as described herein for preparing the compounds of the formula (I) and their salts;

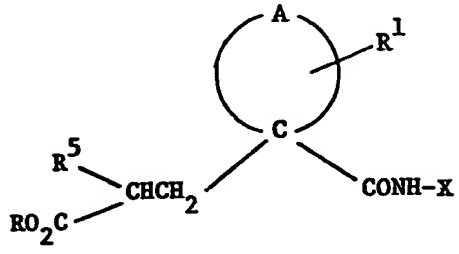
(3) Pharmaceutical compositions comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof of bioprecursor therefor, and a pharmaceutically acceptable diluent or carrier;

(4) A compound of the formula (I), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for use as a diuretic agent for the treatment of hypertension, heart failure and renal insufficiency.

(5) Use of a compound for the formula (I) for the manufacture of a medicament for the treatment of hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menières disease, hyperaldosteronism, pulmonary oedema, ascites, hypercalciuria, glaucoma, asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders, hyperreninaemia and the modulation of gastric acid secretion.

CLAIMS

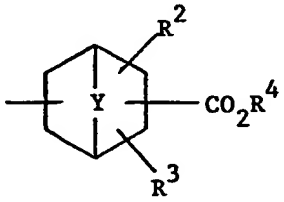
1. A compound having the formula:



(I)

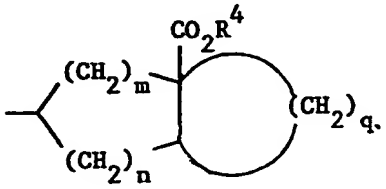
wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

X is a bridged cyclic group of the formula:-



wherein Y is O, CH_2 or $(CH_2)_2$,

or a bicyclic group of the formula:-



wherein each f n and m is independently 1 or 2 and q is an integer of from 3 to 5;

each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

R^2 and R^3 are each independently H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, C_1-C_6 alkoxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$ or a saturated heterocyclic group;

or C_1-C_6 alkyl substituted by one or more substituents chosen from halo, hydroxy, C_1-C_6 alkoxy, C_2-C_6 hydroxyalkoxy, C_1-C_6 alkoxy(C_1-C_6 alkoxy), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, aryloxy(C_1-C_4 alkoxy), heterocyclyl, heterocyclyloxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$, $-CONR^6R^7$, $-SH$, $-S(O)_pR^{10}$, $-COR^{11}$ or $-CO_2R^{12}$;

wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl (optionally substituted by hydroxy or C_1-C_4 alkoxy), aryl, aryl(C_1-C_4 alkyl), C_2-C_6 alkoxyalkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4 alkyl)-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4 alkyl), aryl(C_1-C_4 alkoxy), heterocycyl, C_1-C_4 alk xy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, aryl, heterocyclyl or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{11} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{12} is H or C_1-C_4 alkyl;

and p is 0, 1 or 2;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

2. A pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof of bioprecursor therefor, and a pharmaceutically acceptable diluent or carrier;

3. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for use as a diuretic agent for the treatment of hypertension, heart failure and renal insufficiency.

Published 1989 at The Patent Office, State House, 66/71 High Holborn, London WC1R 4TP. Further copies may be obtained from The Patent Office. Sales Branch, St Mary Cray, Orpington, Kent BR5 3RD. Printed by Multiplex techniques ltd, St Mary Cray, Kent, Con. 1/87